Cervical Cancer Radiotherapy Response in Dr. Hasan Sadikin General Center Hospital

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Abstract
Objective: To determine the response to radiation therapy based on the characteristics of cervical cancer patients who were given radiotherapy at Hasan Sadikin Hospital in 2020.
Methods: The study was conducted using an observational analytic study method with a cross-sectional design, involving 75 cases of cervical carcinoma who were given complete radiation therapy but were not given neoadjuvant chemotherapy or surgery, which were recorded in the medical record at the Central General Hospital (RSUP) Dr. Hasan Sadikin.
Results: Response to therapy had a significant relationship (p< 0.05) with age (p 0.030), histopathological type (p 0.009), and tumor mass size (p 0.042), but had no significant relationship to cervical cancer stage (p 0.055). Further analysis found that the response to radiation therapy at stage III was highly dependent on the size of the tumor mass (p<0.001). Based on the odds ratio calculation, the response to therapy was better in patients aged 35 years 3.44 times compared to patients aged 18-34 years, cervical cancer with squamous type histopathology 5.23 times compared to adenocarcinoma type histopathology, and cervical cancer with tumor mass size. <4 cm 2.86 times compared to tumor mass size 4 cm.
Conclusion: The therapeutic response was better in cervical cancer patients who underwent complete radiation therapy in patients aged 35 years, stage III cervical cancer with tumor mass size <4 cm, squamous type histopathology, and tumor mass size <4cm.

Key words: response to therapy, radiation, cervical cancer

Respon Radioterapi pada Kanker Serviks di Rumah Sakit Umum Pusat Dr. Hasan Sadikin Bandung

Abstrak
Tujuan: Untuk mengetahui respon terapi radiasi berdasarkan karakteristik pasien kanker serviks yang diberikan radioterapi di Rumah Sakit Hasan Sadikin tahun 2020.
Metode: Penelitian dilakukan menggunakan metode studi analitik observasional dengan desain potong lintang, melibatkan 75 kasus karsinoma serviks yang diberikan terapi radiasi komplit tetapi tidak diberikan kemoterapi neoadjuvant maupun tindakan operasi, yang tercatat pada rekam medis di Rumah Sakit Umum Pusat Dr. Hasan Sadikin.
Hasil: Respon terapi memiliki hubungan yang signifikan (p<0,05) terhadap usia (p 0,030), tipe histopatologi (p 0,009), dan ukuran massa (p 0,042), tetapi memiliki hubungan yang tidak bermakna terhadap stadium kanker serviks (p 0,055). Analisis lebih lanjut didapatkan bahwa respon terapi radiasi pada stadium III sangat bergantung kepada ukuran massa tumor (p<0,001). Berdasarkan penghitungan *odd ratio* respon terapi lebih baik didapatkan pada pasien berusia ≥35 tahun 3,44 kali dibandingkan pada usia 18-34 tahun, kanker serviks dengan histopatologi tipe skuamosa 5,23 kali dibandingkan histopatologi tipe adenokarsinoma, dan kanker serviks dengan ukuran massa tumor <4 cm 2,86 kali dibandingkan ukuran massa tumor ≥4 cm.
Kesimpulan: Respon terapi lebih baik pada pasien kanker serviks yang dilakukan terapi radiasi komplit pada pasien berusia ≥ 35 tahun, kanker serviks stadium III dengan ukuran massa tumor <4 cm, histopatologi tipe skuamosa, dan ukuran massa tumor <4cm.

Kata kunci : respon terapi, radiasi, kanker serviks

Introduction

Cervical cancer is cancer that develops in the cells in the cervix. In general, cervical cancer does not cause symptoms in its early stages.[1] Symptoms will appear when the cancer has started to spread. In some cases, cervical cancer is associated with sexually transmitted infections.[2]

The cervix is the lower part of the uterus that is connected to the vagina through the external uterine os. One of the functions of the cervix is to produce mucus or mucus.3 The mucus produced helps the movement of sperm from the vagina to the uterus. The cervix will close during pregnancy and function to keep the fetus in the uterus, and will thin and open during the labor process.

Cervical cancer is one of the deadliest types of cancer in women, in addition to breast cancer.4 In 2010 the estimated number of cases of cervical cancer was 454,000 cases.[2]

The incidence of cervical cancer increased 3.1% annually from 378,000 cases in 1980. Around 200,000 deaths reported to be related to cervical cancer, and 46,000 of them are women aged 15-49 years in developing countries.[2] Cervical cancer has the highest mortality rate in developing countries, and ranks 10th in developed countries or ranks 5th globally. In Indonesia, cervical cancer is ranked second out of the 10 most cancers based on data from Anatomical Pathology in 2010 with an incidence rate of 12.7%.

In 2018 there were 18.1 million new cases of cancer and 9.6 million deaths from cancer worldwide.4 From this cancer incidence, cervical cancer ranks fourth in the incidence of cancer in women worldwide after breast, colorectal and lung cancer.4 Meanwhile, in Indonesia, cervical cancer ranks second in the incidence of cancer with 32,469 new cases and ranks third as the cause of cancer death with 18,729 deaths in Indonesia.4 The prevalence of cervical cancer reaches 0.7 per thousand female population in West Java.[3]

There were 327 cases of cervical cancer in 2017 at the Central General Hospital Dr Hasan Sadikin (RSHS) and cervical cancer is the type of cancer with the second most cases.

The National Guidelines for Medical Services (PNPK) for Cervical Cancer recommends therapy for stage IIB–IIIB cervical cancer by radiotherapy or chemoradiation. However, even with adequate therapy, therapy failure is still found. The incidence of local recurrence at an early stage is about 10-20%, and 40-60% in an advanced local stage.[6]

There are many factors that influence the success of therapy in cervical cancer. The success or failure of the radiation given depends on many factors, including the sensitivity of the tumor to radiation and the response of each patient to radiation. Each cell shows a different response to radiation. This difference in cell sensitivity is influenced by, among others, factors such as age, tumor size, type of histopathology, involvement of surrounding organs, stage, and chemotherapy.

Not many studies have examined cervical cancer patients with radiation response so that an appropriate assessment can be useful for further treatment in the future. In this study, a profile of the characteristics of cervical cancer patients with stage IIB–IIIB will be presented, the histopathological types of cervical cancer, mass size, and stage of cervical cancer given radiotherapy and how the relationship between patient characteristics and cervical cancer is related to the response to therapy in these patients.

Methods

This study was an observational analytical cross-sectional study. The subjects were chosen with total sampling method. This study has been approved and was recommended by Medical Research and Ethical Commitee, Faculty of Medicine, Universitas Padjadjaran,

Bandung, Indonesia.

The subjects of study were all woman with cervix carcinoma who undergo complete external beam radiation therapy with dose 23.4~59.4 Gy without chemosensitizer in outpatient clinics Hasan Sadikin general hospital. Participants were excluded from the study if the cervical cancer patient get neoadjuvant chemotherapy and had been operated, medical record was not complete. Dependent variable was radiation response, complete response if there is no residual lesions and incomplete response if there is residual lesions with reduction of target lesions. Independent variable were age, histopatology type, stadium, tumor mass size. This study was conducted in RS Dr. Hasan Sadikin Gynecologic Clinic, within the period of May - July 2021.

Data analysis in this study was bivariate analysis. The Distribution of data was determined using Chi-square test with calculation of odd ratio. The statistical test to know the effect of age, mass size, histopatology type, and stadium with radiation response was done by using Chi-square test, with $p<0.05$ was considered statistically significant. Then, the correlation between stadium and histopatologic type of cervix carcinoma witg radiation response was analyzed using Fisher exact test with $P<0.05$ was considered statistically significant. Data analysis was done by using SPSS version 25.0 for Windows.

Results

Based on the table above, it can be seen that the characteristics of cervical cancer patients in this study based on the age of cervical cancer patients were generally 35 years (80%). This is in accordance with the epidemiology of cervical cancer which usually attacks women aged 35-55 years. This disease begins with a viral infection that triggers changes in cervical epithelial cell division.

Based on the table, the characteristics of cervical cancer stage are more stage III (84%), which based on histopathological examination mostly show a picture of squamous type cervical cancer (88%) and adenocarcinoma (12%).

In general, based on the response to therapy, cervical cancer patients who were given radiotherapy gave a complete response (64%). Meanwhile, based on the mass size of cervical cancer patients who received the most radiotherapy with a mass size of 4 cm (58.67%).

Based on the table, the age characteristics in the age range of 18-34 years who had a complete response to therapy were 40% of

Table 1 Characteristics of research subject

Variable	Category	N	%
Age	18-35 years old	15	20
	≥ 35 years old	60	80
Stadium	II B	13	17,3
	III	62	82,7
Histopatology	Squamous cell carcinoma	66	88
	Adenocarcinoma	9	12
Mass size	< 4 cm2	31	41,3
	≥ 4 cm2	44	58,7
Radiation response	Complete	48	64
	Incomplete	27	36

cases, while at the age of 35 years a complete response to therapy was obtained in 70% of cases. Based on the stage of cervical cancer, stage IIB received a complete response to therapy in 38.5% of cases, while stage III received a complete response to therapy in 69.36% of cases. adenocarcinoma received a complete response to therapy in 22.2% of cases. Based on the characteristics of the mass size, it was found that cervical cancer mass sizes < 4 cm received a complete response to therapy in 77.5% of cases, while for a mass size of 4 cm a complete response to therapy was obtained in 54.6% of cases.

The table explains that patients aged 18-35 years respond to therapy with a percentage of 40%. Meanwhile, patients aged 35 years generally gave a complete response to therapy (70%). Based on bivariate (chi-square) analysis, it was found that there was a significant relationship between age and response to therapy (p 0.030). With an Odd Ratio value of 0.29, we can conclude that patients aged 35 years have a 3.44 times (1/0.29) tendency to get a complete radiation response compared to patients aged 18-34 years.

The table shows that cervical cancer patients with stage IIB partially gave a complete response to therapy (38.5%) while cervical cancer patients with stage III gave a complete response to therapy (69.4%) and based on statistical tests with Chi-square obtained P value >0.05. We can conclude that there is no significant difference in the stage characteristics of cervical cancer patients on the results of the response to therapy.

The table shows that cervical cancer patients with histopathological type of Squamous cell carcinoma gave a complete

Table 2 Characteristics of Cervical Cancer Patients to Radiation Response

Variable	Category	Therapy response	
		Complete	Incomplete
Age	18-34 tahun	6 (40%)	9 (60%)
	≥ 35 tahun	42 (70%)	18 (30%)
Stadium	IIB	5 (38,5%)	8 (61,5%)
	III	43 (69,4%)	19 (30,6%)
Histopatology	Squamous cell carcinoma	46 (69,7%)	20 (30,3)%
	Adenokcarcinoma	2 (22,2%)	7 (77,8%)
Mass size	< 4 cm	24 (77,5)	7 (22,6%)
	≥ 4 cm	24 (54,6%)	20 (45,4%)

Table 3 Corelation Between Patient Age and Response Therapy

Age	Radiation Response		Total (n=75)	P-value (OR)
	Complete	Incomplete		
18-34 y.o	6 (40%)	9 (60%)	15	0,030*
≥35 y.o	42 (70%)	18 (30%)	60	(0,29)

Table 4 Corelation Between Cervical Cancer Stadium and Response Therapy

Stadium	Radiation Response		Radiation Response	P-value (OR)
	Complete	Incomplete		
• II B	5 (38,5%)	8 (61,5%)	13	0,055#
• III	43 (69,4%)	19 (30,6%)	62	(3,62)

Table 5 Corelation between Histopathologic Type and Response Therapy

Histopatology	Radiation Response		Total (n=75)	P-value (OR)
	Complete	Incomplete		
Squamous Cell Carcinoma	46 (69,7%)	20 (30,3%)	66	0,009#
Adenocarcinoma	2 (22,2%)	7 (77,8%)	9	(8,05)

Table 6 Corelation between Tumor Size and Response Therapy

Mass size	Radiation Response		Total (n=75)	P-value (OR)
	Complete	Incomplete		
• <4 cm	24 (77,42%)	7(22,58%)	31	0,042*
• ≥4 cm	24(54,54%)	20(45,46%)	44	(2,86)

Table 7 Corelation between Histopathological Type and Tumor Size on Response to Therapy in The Stage Iib Group

	Radiation Response		Total (n=13)	P-value
	Complete	Incomplete		
Histopatology				
Squamous Cell Carcinoma	4	1	5	0,032#
Adenocarcinoma	1	7	8	
Mass size				
<4 cm	1	7	5	0,032#
≥4 cm	4	1	8	

response to therapy (69.7%) while cervical cancer patients with histopathological type of adenocarcinoma gave a complete response to therapy (22.2%). Based on bivariate analysis (chi-square), The results showed that there was a significant relationship between the types of histopathology and response to therapy with a p value of 0.009. With an Odd Ratio value of 8.05, we can conclude that patients with the histopathological type of cervical cancer Squamous cell carcinoma have a tendency of 8.05 times to get a complete radiation response compared to patients with the histopathological type of cervical cancer adenocarcinoma.

The table explains that patients with a mass size of < 4 cm gave a complete response to therapy of 77.42% and patients with a mass size of 4 cm also gave a complete response to therapy of 54.54%. Based on bivariate (chi-square) analysis, it was found that there was a significant relationship between tumor mass size and response to therapy with a p value of 0.042. With an Odd Ratio value of 2.86, we can conclude that patients with cervical cancer mass size <4 cm have a 2.86 times tendency to get a complete radiation response compared to patients with cervical cancer mass size 4 cm.

Stadium IIB group

Based on bivariate analysis (Fishers Exact Test), it was found that there was a significant relationship between Histopathological Type (p 0.032), and Size (p 0.032) on response to therapy (p <0.05).

Stadium III group

Based on bivariate analysis (Fishers Exact Test), in the stage III group, it was found that

Table 8 Corelation aetween Histopathological Type and Tumor Size on Response to Therapy in the Stage Iii Group

	Radiation Response		Total (n=61)	P-value
	Complete	Incomplete		
Histopatology type				
Squamous Cell Carcinoma	42	19	61	1,000#
Adenocarcinoma	1	0	1	
Mass size				
≥4 cm	20	19	39	<0,001*
<4 cm	23	0	23	

there was no significant relationship between Histopathological Type (p 1.00) and response to therapy (p>0.05). Based on bivariate (chi-square) analysis, it was found that there was a significant relationship between size (p<0.001) and response to therapy (p< 0.05).

Discussion

Radiation therapy aims to damage tumor cells in the cervix and kill tumor cells that spread to the parametrium and lymph nodes in the pelvis. When exposed to radiation, the tissue will absorb radiation energy and cause atomic ionization. Chemical and biochemical changes can result from the ionization of these atoms so that they will cause cell damage. Cell damage that occurs can be in the form of chromosomal damage, mutations, slowing of cell division and loss of the ability to produce.[21] In this study, several characteristics related to radiation response were assessed.[22]

Based on the results of the data obtained from the relationship between age and radiation response, it shows that patients aged 18-35 years respond to therapy with a percentage of 40%. Meanwhile, patients aged 35 years generally gave a complete response to therapy (70%). And based on bivariate (chi-square) analysis, it was found that there was a significant relationship between age and response to therapy (p 0.030). With an Odd Ratio value of 0.29, we can conclude that patients aged 35 years have a 3.44 times (1/0.29) tendency to get a complete radiation response compared to patients aged 18-34 years. This is in accordance with previous studies which stated that the average age of patients was 47-52.2 years. 12 The age of cervical cancer patients was between 40-59 years.[1]

The results of the study based on the relationship between stage and response to therapy showed that cervical cancer patients with stage IIB partially gave a complete response to therapy (38.5%) while cervical cancer patients with stage III gave a complete response to therapy (69.4%) and based on statistical tests with Fishers Exact Test obtained P value> 0.05. We can conclude that there is no significant difference in the stage characteristics of cervical cancer patients on the results of the response to therapy. This explains that therapy with radiotherapy provides a good therapeutic response to various stages of cervical cancer at stage II B or stage III . However, this is different from the research conducted by Duenas et al (2010) which concluded that stage IIB cervical cancer patients received a better complete radiation response compared to stage III.[14]

Then further analysis was carried out on the two population groups of stage IIB and stage III. In the stage IIB group, it was found that there was a significant relationship between histopathological type (p 0.033), and size (p 0.042) on response to therapy (p<0.05), while in the stage III group the results showed that there was no significant

relationship between histopathological type (p 1.00) on response to therapy (p>0.05) but there was a significant relationship between size (p<0.001) and response to therapy (p < 0.05). From these results we can conclude that the higher the stage, the response to therapy will be very dependent on the size of the tumor mass.

This study showed that cervical cancer patients with histopathological type of Squamous cell carcinoma gave a complete response to therapy (69.7%) while cervical cancer patients with histopathological type of adenocarcinoma gave a complete response to therapy (22.2%) Based on bivariate analysis (Fishers exact test) , it was found that there was a significant relationship between the types of histopathology and the response to therapy with a p value of 0.009. With an Odd Ratio value of 8.05, we can conclude that patients with the histopathological type of cervical cancer Squamous cell carcinoma have a tendency of 8.05 times to get a complete radiation response compared to patients with the histopathological type of cervical cancer adenocarcinoma. In a study conducted by Bahar et al., it showed that about 71% of the complete response to therapy was in the histopathological type of squamous cervical cancer.[12]

Survival in patients with cervical cancer with a larger tumor size will be worse than in patients with a smaller mass of cervical cancer. In this study, it was found that patients with a mass size of <4 cm gave a complete response to therapy of 77.42% and patients with a mass size of 4 cm also gave a complete response to therapy of 54.54%. This shows that cervical cancer mass size <4 cm has a better therapeutic response than cervical cancer mass size 4. Other studies also mention that in general, small tumor sizes have a better response to therapy by controlling certain radiation doses compared to larger tumors.24 In this study we can also conclude that patients with cervical cancer mass size <4 cm has a tendency of 2.86 times to get a complete radiation response compared to patients with cervical cancer mass size 4 cm.

This can be explained that the tissue when exposed to irradiation radiation, will absorb radiation energy and will cause ionization.

Conclusion

The age characteristics of cervical cancer patients who were given radiotherapy at Hasan Sadikin Hospital in 2020 were mostly at the age of 35 years, which was 80%. The most stages of cervical cancer given radiotherapy at Hasan Sadikin Hospital in 2020 was stage III, which was 82.7%. The histopathological description of cervical cancer that was given radiotherapy at Hasan Sadikin Hospital in 2020 was mostly in the squamous histopathological type, which was 88%. The size of the mass of cervical cancer that was given radiotherapy at Hasan Sadikin Hospital in 2020 was the most with a mass size of 4cm, namely 58.7%. The response to radiotherapy of cervical cancer patients who were given radiotherapy at Hasan Sadikin Hospital in 2020 was the most complete response, which was 64%. Patient age, histopathological description, and cervical cancer mass size in cervical cancer patients were associated with radiation response in cervical cancer patients who were given radiotherapy at f yHasan Sadikin Hospital in 2020. Meanwhile, cervical cancer stage had no significant relationship with radiation response in cancer patients. cervical cancer given radiotherapy at Hasan Sadikin Hospital in 2020.

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